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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,913	12/22/1998	RODERICK L. HALL	98.736	2461

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/218,913	HALL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,14 and 16-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 14, and 16-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 31, 2004 has been entered.

The application has been amended as requested in the communication filed March 31, 2004. Accordingly, new claims 19-29 have entered.

Claims 1-10, 14, and 16-29 are under consideration as they pertain to SEQ ID NO: 52.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Rasche *et al.* [IDS, paper number 16, reference number 7, *Arznemittel-Forschung* 25 (1) 110-116 (1975)].

Rasche *et al.* teach the use of aprotonin, a Kunitz-type serine protease, isolated from bovine organs and formulated in a commercially available pharmaceutical composition known as TRASYLOL® in the treatment of chronic obstructive bronchitis. TRASYLOL® inhibits the symptoms of the disease and is well tolerated by patents (claims 1 and 10), see English summery on page 116, right column. Also, they teach the administration of aprotinin by inhalation to the lungs (claims 2-4). Claims 5-9 are included in this rejection because the formulation of TRASYLOL® is not described in the article, and the examiner could not ascertains many of the details of experiments in the article because it is written in German.

In response to the above rejections, Applicants reiterated their previous arguments that the cited reference does not disclose every element of the claim because they do not teach a method for accelerating mucocilliary clearance as presented in the instant claims.

Applicants' arguments filed 3/31/04 have been fully considered but they are not deemed to be persuasive. The specification defines the phrase "mucocilliary dysfunction" as the inability of ciliated epithelium to clear mucus and sputum in lung airway which is a serious complication of chronic obstructive lung diseases such as chronic bronchitis (CB), bronchiectasis, asthma, and specially, cystic fibrosis (CF), see

page 1, lines 14-17. Rasche *et al.* teach the use of aprotonin, a Kunitz-type serine protease, to treat an obstructive lung disease such obstructive bronchitis and emphysema, see the paragraph bridging pages 1 and 2. Also, they teach that a shortage of local protease inhibitors can arise in the bronchial area causing chronic obstruction in the airways for many years. The results obtained Rasche *et al.* clearly show that the application of the protease inhibitor relive the dysfunction and improve the patent conditions. It appears that the drop of in airway resistance and the liquefaction of viscous sputum are clinical observation resulting from accelerating mucocilliary clearance, I. e., increasing the clearance of mucus and sputum from the lung airway. Thus, accelerating mucocilliary clearance is an inherent property of the method taught by Rasche *et al.* Applicants have the burden of distinguishing their invention from that of the prior art. Thus, the claims remain rejected.

The following is a quotation of 35 U.S.C. § 103, which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 3-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Rasche *et al.* [IDS, paper number 16, reference number 7, *Arznemittel-Forschung* 25 (1) 110-116 (1975)] in view of the state of the art.

Rasche *et al.* provide one of ordinary skill in the art with motivation of using aprotinin composition for the treatments of lung conditions characterized by improper mucociliary clearance such as in the case of chronic obstructive bronchitis. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to

formulate aprotinin in a composition appropriate for administration to human lungs. One of ordinary skill in the art would have been able to prepared several aersolizable compositions such as dry powder, suspensions, or solutions of aprotinin and use them for the treatment of indicated conditions by the administration of the composition directly to the lungs air ways. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

In response to the above rejections, Applicants continue to argue that the examiner failed to establish a *prima facie* case of obviousness because Rasche *et al.* does not suggest an accelerated rate of mucocilliary clearance by administering a composition comprising a Kunitz-type serine protease inhibitor.

Applicants' arguments filed 3/31/04 have been fully considered but they are not deemed to be persuasive. The examiner agrees with the applicants that Rasche *et al.* does not suggest an accelerated rate of mucocilliary clearance by addminestring a composition comprising a Kunitz-type serine protease inhibitor, but the acceleration of the rate of mucocilliary clearance is inherent property of the method taught by Rasche *et al.* Rasche *et al.* teach the claimed method, and provide one of ordinary skill in the art with a motivation to deliver the pharmaceutical composition directly to the airways. They write (see last paragraph of the translated document on page 7):

> We based this on our investigations and of other authors who showed that most biochemical reactions, which lead to airway obstruction, occur locally in the bronchial area, and therefore would be better influenced by inhalation therapy.

Inhalation therapy encompasses all means of administering drug to the airways such as aerosol, aerosol suspension, and powder inhaler, which can be delivered by any kind of nebulizer, and non-toxic propellant. The ordinary skill in the art would have had the experience, and the knowledge to formulate any chemical compound in an aerosol, aerosol suspension or dry powder inhaler and the means to deliver them as evident by the availability of many drugs on the market in these forms. Also, Rasche *et al.* provide one of ordinary skill in the art with an expectation of success as they teach a method of treating chronicle bronchitis with Kunitz-type inhibitor. Thus, the examiner has met his burden by establishing a *prima facie* case of obviousness, and the claims remain rejected.

Claims 14, and 16-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Delaria *et al.* (J. Biol. Chem. 1997, 272 (18), 12209-12214) in view of the state of the art as exemplified by Rasche *et al.* [IDS, paper number 16, reference number 7, *Arznemittel-Forschung* 25 (1) 110-116 (1975)], Fritz *et al.* (U. S. Patent 5,407,915), and O'Riordan *et al.* (IDS: Am. J. Respir. Crit. Care Med Vol. 155, pp. 1522-1528).

Delaria *et al.* teach the expression in SF9 cells and characterization of a soluble placental bikunin, having N-terminus sequence ADRER- and 170 amino acid residues corresponding to SEQ ID NO: 52 of the instant application, see the abstract and page 12211, the first two paragraph of the result section. Also, they teach the 170 amino acid

residue protein contains two Kunitz-type domain corresponding to residues 7-64 and 102-159. Table 1 on page 12213 shows the inhibition constants for bikunin of SEQ ID NO: 52, two polypeptide corresponding to the two Kunitz domain of bikunin, and aprotinin inhibition of various serine proteases. The results indicates that bikunin and its Kunitz fragments are potent inhibitors of serine proteases. It should be noted that bikunin1-170 is expressed in SF9 insect cells, and therefor is expected to be glycosylated. Delaria *et al.* do not teach the use of bikunin1-170 in the treatment of any diseases or conditions.

The teachings of Rasche *et al.* are summarized above.

Fritz *et al.* teach the desirability of low molecular weight human protein having a Kunitz-type domain for the treatment of diseases related to excess activity of neutrophil elastase such as emphysema, shock lung and ARDS, see column 1, lines 24-62. They teach a human inter-α-trypsin inhibitor ITI (bikunin) that differs from the bikunin of the instant application. Said inhibitor contains two Kunitz domain corresponding to residues 22-77 and 78-147 each of which is capable of inhibiting serine proteases, see the paragraph-bridging column 1 and 2. Also, they teach various analogs of bikunin and its Kunitz domains that are specific inhibitors, see examples 1-5, and the formulation of the inhibitors into pharmaceutical compositions, see from column 4, line 37 through column 6, line 48, in particular column 5, lines 40-46.

O'Riordan *et al.* teach that antigen-induced bronco constriction is associated with impairment of mucociliary clearance, and the contribution of neutrophil elastase to the development to the development of such a condition.

Rasche *et al.* provide one of ordinary skill in the art with motivation and expectation of success to develop a method for treatment of a of lung conditions characterized by improper mucociliary clearance such as in the case of chronic obstructive bronchitis using composition containing Kunitz-type inhibitor. Fritz *et al.* motivate one of ordinary skill in the art to use human proteins having low molecular weigh such as bikunin. Delaria *et al.* provide one of ordinary skill in the art with motivation to use the placental bikunin expressed in mammalian cells in the pharmaceutical composition as they teach a water-soluble glycosylated human bikunin. Thus it would have been obvious to one of ordinary skill in the art at the time of invention to formulate the glycosylated human protein of SEQ ID NO: 52 taught by Delaria *et al.* in a pharmaceutical composition by well known methods in the art such as those taught by Fritz *et al.* and use the composition in a method to treat a condition related to the impairment of mucociliary clearance similar to that taught by Rasche *et al.* (claim 13, and 16). It should be noted that one of ordinary skill in the art would have been able to prepared several aersolizable compositions such as dry powder, suspensions, or solutions of SEQ ID NO: 52 and use them for the treatment of indicated conditions by the administration of the composition directly to the lungs air ways. Also, it should be noted all the cystine residues cited in claim 18 are found in SEQ ID NO: 52,

and therefore, the protein is expected to form the requisite disulfide bonds (claims 17 and 18). New claims 19-29 are included in this rejection because they are directed to the same subject matter of the previously rejected claims. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

In response to the above rejections, Applicants continue to attempt to discredit each individual reference by indicating that they do not teach the invention.

Applicants' arguments filed 3/31/04 have been fully considered but they are not deemed to be persuasive. The cited prior art clearly contains all the teaching required to carry out the claimed invention including the amino acid sequence of SEQ ID NO: 52. Also, the prior art provides motivation to incorporate all the elements of the claimed invention. Fritz *et al.* motivate one of ordinary skill in the art to use human proteins having low molecular weigh such as bikunin. Delaria *et al.* provide one of ordinary skill in the art with motivation to use the placental bikunin expressed in mammalian cells in the pharmaceutical composition as they teach a water-soluble glycosylated human bikunin. Rasche *et al.* teach a method of treating chronicle bronchitis with Kunitz-type serine protease inhibitor, see above. As indicated by the applicant O'Riordan *et al.* suggested that elastase inhibitor may be useful in protecting against mucocilliary dysfunction, see page 41 of the response to the first Office action. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 14, and 16-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 15-18 of copending Application No. 09/441,966 (966).

Claims 1-10, 14, and 16-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 15-18 of copending Application No. 09/441,966 (966). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-10 of the instant application a generic claims drawn to a method of accelerating the rate of mucociliary clearance comprising administering a composition comprising Kunitz-type serine protease inhibitor. Also, claim 14 from which claims 16-18 are dependent are limited to a specific Kunitz-type serine protease inhibitor identified by amino acid sequences. Claims 1-10 and 15-18 of the '966 application are drawn to the same method. The claims of the '966 application are narrower in scope because the broadest claim define amino acid sequences. Claim 1 of the '966 application contain SEQ ID NO: 52, which is the elected species for prosecution in the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to the above rejection, Applicants have not traverses the above rejection or filed a terminal disclaimer. They have requested to hold the rejection in abeyance until allowable subject matter is indicated. The rejection will remain on record until further action by the applicants.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner